ABSTRAK

Pendahuluan : Kanker buli merupakan kanker urogenital ketiga tersering pada pria dengan *survival rate* dalam 5 tahun mencapai 77%. Penelitian dilakukan untuk meningkatkan efikasi tatalaksana termasuk cisplatin sebagai regimen utama kemoterapi. Peran metformin pada tatalaksana kanker buli masih dipertanyakan. **Tujuan :** Untuk menilai efikasi metformin-cisplatin dalam menurunkan viabilitas dan *late apoptosis* sel kanker urothelial (UCCC)**. Metode :** UCCC (*cell line 5637* CLS Jerman) dibiakkan di laboratorium hingga mencapai konfluensi 80% dan terbagi dalam 6 kelompok: control-media, control-UCCC, UCC-metformin-cisplatin IC-50 (1/4 x CC), UCCC-metformin-cisplatin 1/2dosis dari IC-50(1/2 x CC) dan UCCC-metformin-cisplatin dosis ganda IC-50(2xCC). Seluruh kelompok UCCC kecuali CM, diinkubasikan dengan metformin-cisplatin dosis IC-50 berbeda selama 48 jam. IC-50 metformin-cisplatin ditentukan berdasarkan MTT assay yang dilakukan sebelumnya (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Penilaian efek farmakodinamik menggunakan *software CompuSyn* dari *The ComboSyn, Inc*. Persentase *late apoptosis* (%LA) pada tiap kelompok diukur menggunakan metode FACS. SPSS Ver.25 digunakan untuk membandingkan dan menganalisa hubungan antar kelompok (signifikan bila $p < 0.05$). **Hasil :** Hasil MTT assay cisplatin-metformin menunjukkan tren penurunan viabilitas dari sel kanker buli dengan peningkatan dosis dan uji statistik menunjukkan signifikansi dari seluruh kelompok perlakuan baik dibandingkan kontrol dan rerata antar grup ($p < 0.05$). Penilaian efek farmakodinamik kombinasi menunjukkan hasil antagonistik ringan (CI>1). Hasil FACS menunjukkan perbedaan yang signifikan antara kelompok ¼xCC (68.03±0.675, p=0.0001), $^1/_2$xCC (74.23±0.342, p=0.0001), 1xCC (77.49±0.556, p=0.0001), 2xCC (70.06±0.278, p=0.0001) dan CU (13.2±1.24). Analisa post hoc menunjukkan peningkatan efek berdasarkan dosis. Persentase apoptosis meningkat pada konsentrasi IC-50 kedua obat meningkat pada kelompok 1/4 x IC-50, 1/2 x IC-50 dan 1 x IC-50. Persentase *late apoptosis* pada dosis 2xIC50 lebih rendah dibandingkan 1xIC-50, yang kemungkinan akibat proses nekrosis. **Kesimpulan :** Penelitian ini menunjukkan kombinasi metformin-cisplatin efektif menurunkan viabilitas dan menginduksi *late apoptosis* sel kanker urothelial. Efikasi lebih tinggi diperoleh dengan meningkatkan dosis IC-50 Metformin-cisplatin.

Kata kunci: kanker buli, sinergitas, cisplatin, metformin.

ABSTRAK

Introduction Bladder cancer (BCa) is considered as the 3rd most common urogenital cancer in Men with 5 years average overall survival of xx%. Many researchers have focused on increasing the efficacy of bladder cancer management, including cisplatin as the main regiment for chemotherapy. The role of metformin in bladder cancer management is currently controversial. **Aim :** To test the efficacy of metformin-cisplatin in inducing late apoptosis of urothelial carcinoma cell line (UCCC). **Material and methods** The UCCC was obtained from CLS (Germany) and cultured at our laboratory until confluency of 80% was reached and divided into groups 6 : controlled-medium (CM), controlled-UCCC (CU), UCCC-metformin - cisplatin standard IC-50 (1 x CC), UCCC-metformin - cisplatin 1/4 dosage of IC-50 (1/4 x CC), UCCC-metformin - cisplatin 1/2 dosage of IC-50 (1/2 x CC) and UCCC-metformin - cisplatin double dosage of IC-50 (2 x CC). All groups of UCCC except CM were incubated with metformin-cisplatin of different IC-50 dosages for 48 hours. The inhibition-concentration-50 (IC-50) of metformin and cisplatin in this study were previously determined using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). The late-apoptosis percentage (% LA) cells in each group were measured using flowcytometry acquisition cell sorting (FACS) method. SPSS ver25 were used for comparison and analysis between groups and considered significant if $p<0.05$. **Results** FACS results showed significant differences of % LA between 1/4 x CC (68.03±0.675, p=0.0001), 1/2 x CC (74.23±0.342, p=0.0001), 1 x CC (77.49±0.556, p=0.0001), 2 x CC (70.06±0.278, p=0.0001) and CU (13.2±1.24) groups. The post-hoc analysis have also proven a dose-escalation effect where % of LA increased as the IC-50 concentration of both drugs were increased in 1/4 x IC-50, 1/2 x IC-50 and 1 x IC-50 groups. However, we also observed that although the 2 x IC-50 result showed lower % LA than 1 IC-50 group, this phenomenon was due to the necrosis process of cells rather than late apoptosis as shown in the FACS results. **Conclusion** Our study emphasize that the combination of metformin and cisplatin were effective to induce late apoptosis in urothelial carcinoma cell line. The higher efficacy can be achieved by increasing the IC-50 dosage of metformin and cisplatin.

Keywords: Ca Buli, synergism, cisplatin, metformin.